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*Kamman, G. R.: Fatigue as a Symptom in Depressed Patients, Journal-Lancet 65:238 (July) 1945.

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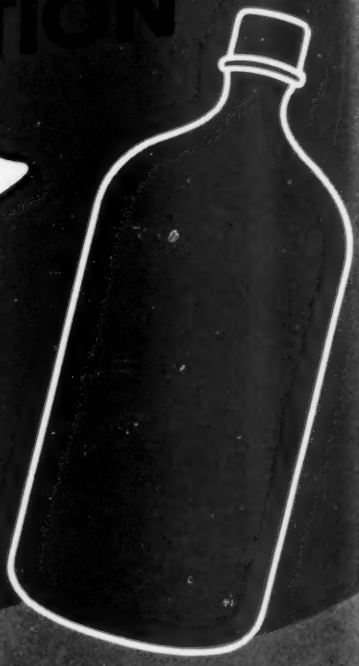

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EDITORIAL

FOOD AND WORLD POPULATION

OUR nation is faced today with pleas for food coming from almost every country in the world. There are of course a few countries such as the United States that produce food surpluses but these surpluses are far short of the acute need resulting in mass starvation and undernourishment throughout the world.

Nutritionists tell us that undernourishment begins at 2000 calories daily, lowered resistance to disease at 1600 and starvation is certain if the available calories drop to 800 a day. The unhappiness and misery suffered by a person forced to live on a calorie deficient diet was observed in many prisoners of war; disease is rampant and both mind and body deteriorate until death mercifully ends one's agony. Unfortunately, death from partial starvation is slow and agonizing with the instinctive will to live fighting a desperate but losing battle.

It would seem a reasonable thing to study the world food problem more scientifically rather than simply to give some small part of our food supply in the hope that it will minimize hunger and suffering in the needy countries. The problem is not that simple and such food shipments may in some places only aggravate the condition. This may seem a strange and paradoxical statement until the facts of the case are given some thought. The U. S. Soil Conservation Service has stated that there are only about four billion acres of arable land in the world to fill the needs of two billion people. This averages to two acres per capita. Nutritionists claim that it takes at least two and one-half acres per capita to provide even an adequate diet. Of the four billion acres only about one billion would really constitute what American farmers consider really good productive soil. Some increase in the productivity of soil may be brought about by technological advances but no rapid increase in the food supply seems likely by this means. Farmers are not too ready to adopt new methods and technics, and government planning and regimentation has not proven very successful in the instances where it has been tried.

We were greatly impressed with one aspect of the problem recently discussed in the *Bulletin of the Sydney Technical College Chemical Society.*

The author by quoting certain facts and figures taken from the *Journal of Heredity* draws attention to the hopelessness of the situation unless the excessively high birth rate in certain countries, e. g. India, is curtailed. India is notorious for its births and famines, but how many people have associated these as cause and effect?

The following excerpt from the *Journal of Heredity* states very succinctly the obvious truth:

> *"The Emergency Committee evidently does not know—or dares not face the central crucial fact about the situation in India —that competent authorities are unanimous in their conviction that the age-old problem of famine in India cannot be solved by food imports. It may seem paradoxical, but it is none the less true, that the total suffering in terms of numbers dead and man-hours spent in dying is inevitably increased by food shipments. Those who get the food have a brief respite. But the number of people pushes up like a relentless spring. Next month, perhaps, surely next year, or the year after, with awful certainty, these excess lives will be cruelly snuffed out by starvation and disease.*
>
> *"What is wrong with India is not the war, which touched the economy of India relatively slightly, even though Indian troops fought gallantly in many parts of the world. Nor is it the 1943 famine. What is wrong with India is her cruel, relentless, inhuman fertility. 'Mother India,' indeed! A mother who brings forth endless millions of children inevitably doomed to starve. A mother who smothers the living in a swarm of unborn whose arrival seems as inevitable as the rising of the sun. That is the real trouble with India. Until this pathological procreant mother mends her reproductive ways, nothing can be done to help her."*

Intelligent people the world over are giving careful thought to the social and economic problems attached to uncontrolled births which invariably take place in the lowest stratum of society. Children so born are almost certainly predestined to suffer poverty, lack of opportunity and many other social detriments. Education of the masses seems the only answer to this problem since it is contrary to our fundamental concepts of basic human rights to adopt forced sterilization as a means of control. Here again we, however, are confronted with prejudice and bigotry, for many people, although practicing birth

control themselves, speak loudly against it, claiming it to be an immoral act.

Social and economic problems will never be solved as long as man is guided by prejudice, superstition and bigotry. They can be solved only by the application of the scientific method which seeks to correlate the facts based on observation and study and then fit them together into a picture that is both unprejudiced and impersonal.

L. F. TICE.

USE AND MISUSE OF HORMONES

By W. H. Stoner *

RESPONSIBILITY for misuse of hormones is divided among manufacturer, pharmacist, physician and patient. Among the undesirable practices of the manufacturer, is the marketing of products purporting to contain hormone substances, but really entirely inactive, as powdered glands of internal secretion and even powdered meat from non-glandular sources. Ground kidney, breast, prostate, intestine, spleen, and even skin have been promoted as hormone products. The criteria which determine the endocrine status of a tissue are that its removal causes a definite train of symptoms, and that these symptoms are overcome by replacement therapy with that tissue or its extract.

Another factor leading to misuse of hormones for which the manufacturer is responsible, is the present confusion in expression of potencies of the various hormone preparations. In the earlier days of endocrinology when hormones were available only as impure extracts of the gland, biologic assay was necessary and potencies had to be expressed in terms of biologic units, rat units, international units, Clauberg units, Allen-Doisy units, etc. Similarly, vitamin potencies were expressed in biologic units up until the time the chemical natures of the vitamins became known. Then the potencies were better expressed in terms of weight. Similarly, potencies of hormones, as they become chemically identified and synthesized are best expressed in unequivocal terms of weight, milligrams, gamma, etc. Much confusion in posology could be avoided if rat units and international units of estrogenic hormones were dropped and only milligrams used as in the cases of corpus luteum, male sex and adrenocortical hormones.

Still other complications of the subject of practical endocrinology, culpability for which rests on the manufacturer, are the multiplicity and duplication of products that flood the hormone market. Among the factors leading to this unnecessary multiplicity of products are undue retention on trade lists of ridiculously low and ineffectual dosage forms, combinations in fixed proportions of two or more hor-

* Medical Research Division, Schering Corporation, Bloomfield, N. J.
Read before Philadelphia Section, American Pharmaceutical Association, Nov. 21, 1946.

mones, and attempts to make all hormones available for administration by every known route of getting drugs into the human body. For example, when progesterone was first available, it was issued in ampules of one-tenth milligram, whereas the present minimal effective dose is five milligrams, and probably more frequently, the ten milligram ampule is used; and a few physicians prefer twenty-five milligram ampules. Reluctance on the part of the manufacturer to drop the older, useless and small dosage forms clutters the pharmacy shelves with products prescribed by only a very few physicians. Prompt striking of these dosage forms from trade lists would promptly wean these die-hard physicians from their use in preference to the more modern, larger, active dosage forms. In regard to combinations of active hormone products in fixed proportions, the Council on Pharmacy and Chemistry of the American Medical Association has frequently gone on record as being opposed to any such combinations as irrational, with the statement that the several constituents of such products are better prescribed separately in the dosages indicated.

Still another factor leading to multiplicity of products is the practice of developing preparations of each known hormone for administration by every known route, parenteral, oral, inunction, subcutaneous implantation, sublingual, and by suppositories or bougies.

Another deficiency of the manufacturer is his frequent misconception that purified hormone principles are invariably more potent than more crude extracts. The chemist may spend much time, energy and money in preparing highly purified crystalline compounds from glandular extracts only to find that his intermediates, or even the crude extracts, have greater potency. This was found particularly with the comparison between thyroid and thyroxin, desoxycorticosterone and cortical extracts and purified gonadotropic hormones from pregnant mare serum and from pregnancy urine when compared with the same substance fortified by a principle obtained from anterior pituitary gland as a synergist.

Probably the most deplorable contribution of the manufacturer to defamation of endocrinology is the recent incorporation of various hormones into cosmetic preparations. When it was shown definitely that steroid hormones, such as estradiol and methyl testosterone, are effectually absorbed through the skin by inunction, the cosmetic manufacturer immediately saw possibilities for volume sales to the laity of products advertised to contain such hormones, but really con-

taining so little as to be entirely inactive and harmless. Therapeutic use of really active hormone ointments should be under the direction of the physician. Already the lay press carries ads for such products, and if the manufacturers can find a way of circumventing the vigilance of the Federal Trade Commission, the radio will soon be blaring such ads over the air.

Important as may be the contributions of the manufacturer to the misuse of hormones, those of the physician are of far more vital importance to the patient. Probably the most harmful practice in clinical endocrinology is the assumption of hormone deficiency without clinical or laboratory confirmation. Many patients with vague, indefinite symptoms, usually largly subjective, are assumed to be hypogonadal, hypothyroid, etc., and treated accordingly without sufficient evidence of deficiency. The harm done by administration of hormones in these cases is trifling compared to the harm that may result from lack of recognition of the real condition, and failure to apply the treatment for it.

Injudicious choice of product often leads to disappointing results. For example, a physician who chooses his products solely on the price basis is destined to occasional disappointment. Use of stilbestrol and other ersatz products in place of the physiologic hormones may cause nausea, vomiting, permanent liver damage and loss of the patient by the physician. Many physicians even today are continuing to use so-called hormone products without potency. When these contain thyroid, they are as active as the thyroid they contain, and thyroid alone would be preferable. On the other hand, the over-enthusiastic endocrine therapist may indulge in too large doses. In the early days of insulin, as high as one thousand units were administered at one dose in cases of diabetic coma. This therapy was irrational because seventy-five to one hundred units of such a dose were untilized and the remainder eliminated. No greater effect could be obtained in lowering blood sugar with a thousand than with a hundred units of insulin. Similarly today, it is probable that huge doses of sex hormones are largely wasted. The most rational method of dosage is to simulate as closely as possible the continuous, smooth curve, physiologic production of the hormone by giving small doses frequently. The manufacturer has introduced several artifices to this end. For example, steroid hormones are combined with organic acids as esters in order to decelerate their absorption and their metabolism. Insulin is combined with protamine, globulin, etc., for the same purpose. This

depot therapy is most effectively accomplished by subcutaneous implantation of crystals or pellets of hormones. These deposits act as artificial glands and yield their hormones in continuously regular amounts for long periods. Still another artifice is to administer hormornes sublingually at frequent intervals during the day, or to administer low potency oral tablets several times a day. Parenteral injection, even of the least quickly de-esterified combination, results in peaks and valleys in blood hormone content. The customary three injections a week do not parallel very closely the normal hormone production.

Perhaps the most serious untoward result from over-dosage of hormones is a mild accentuation of a normal physiologic function, because the body has the benefit of a physiologic protective mechanism against overages of substances produced naturally in the body. But with substitute "hormones" against which no protective physiologic mechanism is available, over-dosage may produce much more serious and permanent bad results. In cases of proved hormone deficiency, intensive substitution therapy should be employed until the deficiency symptoms are controlled, after which smaller doses may be used as maintenance therapy. This is especially true in menopause where it is desirable to give the patient assurance that hormone therapy will control her symptoms. Unless prompt relief is obtained, the patient is likely to lose all faith in therapy and her condition will be aggravated.

The physician must bear in mind that hormones are extremely active substances. Dosages are in milligrams and gamma, making them comparable in potency to the most poisonous alkaloids, strychnine, etc. Fortunately, the margin of safety, spread between therapeutic effective and toxic doses, is greater with hormones than with the toxic alkaloids. Otherwise poor endocrine therapy would be a more serious matter. The tendency of the body toward homeostasis soon readjusts the delicate interbalance of glands following even the most clumsy dosage errors of the physician.

Seldom, if ever, is there a uniglandular abnormality. Always two or more glands are involved in an endocrinopathy and it is frequently almost impossible to determine which gland is basically at fault, so that therapy may be applied at source. From this standpoint, therefore, polyglandular therapy is sometimes justifiable when accurate specific diagnosis is impossible. Administration of active products of the several glands is a diagnostic test to determine to

which gland the symptoms may be attributed. The constituents of the polyglandular remedy representing glands in which no deficiency existed, do little if any harm because they are administered in amounts much smaller than the normal production of the gland.

Injudicious choice of route of administration may lead to poor results. The physician may yield to his patient's whim as to whether the hormone is to be given by mouth, parenterally, by inunction, etc. There is always a best way of administering the hormone which should be decided by the physician, and not purely on his or the patient's convenience. Some physicians use parenteral therapy exclusively so as to keep intimate control of the patient and to multiply the number of office visits. If purely local effects are wanted, hormones may be applied locally as in treatment of juvenile vaginitis with estrogen bougies, or kraurosis vulvae and undeveloped breast with estrogen ointments. Greater concentration is yielded by applying the hormone locally than by systemic administration.

Common error in hormone therapy is confusion of the indications for stimulation and substitution therapy. An endocrine gland cannot be stimulated to increased production by administration of preparations of that gland. In fact, administration of a hormone usually decreases the physiologic activity of the corresponding gland, at least temporarily. The senescent ovary cannot be whipped to renewed activity by administration of the ovarian hormone. Spermatogenesis is diminished by certain dosages of male sex hormone; but both the testis and the ovary may be stimulated by administration of active preparations of gonadotropic hormones from the pituitary or of anterior pituitary-like hormones from pregnant mare serum and pregnancy urine. Unfortunately, no hormone stimulation therapy is available for the pituitary, although proper x-ray dosage is of some value.

The physician today in his endocrine therapy can follow one of two courses, dependent upon his equipment, educational and physical. If he has a thorough training in endocrinology and laboratory facilities for all modern diagnostic procedures, he can usually fix responsibility upon one gland as the primary cause of a train of endocrinopathic symptoms. He is then in position to treat the patient by administration of either substitution or stimulation organotherapy. However, on the other hand, if his experience in endocrinology and his diagnostic facilities are limited, he may resort to the method of the therapeutic test by guessing which of the several glands of internal secretion, if

any, is involved and applying endocrine treatment on that basis, assuming his diagnosis to be correct in case of improvement and incorrect if no improvement results in a reasonable period. This latter method of trial and error is less efficient, slower and more prone to untoward results. The best endocrinology cannot be practiced unless the physician is equipped for the following diagnostic procedures; thorough physical examination, particularly for endocrine stigmata, such as changes in voice, distribution of hair and fat, complete examination of genital system, gynecologic and urologic, x-ray examinations, particularly of the epiphyses, basal metabolic rate determinations, examinations of the urine for gonadotropic hormone, estrogen, 17-ketosteroid, pregnandiol, sodium, potassium, chlorides, cholesterol, sugar, non-protein nitrogen and creatinine, and of the blood for all its clinically significant chemical constituents, vaginal smears and biopsies and endometrial biopsies.

The physician often misapplies the results of animal experimentation to his clinical practice, assuming that hormones have the same actions in human beings as in rats, mice, guinea pigs, pigeons, frogs, etc. In general this assumption is correct, particularly in the various classes of mammals, but even within this classification there are occasionally wide discrepancies. For example, when the anterior pituitary-like hormone extracted from pregnant mare serum was first made available, it was reported to produce ovulation in the woman as in the rabbit, and that a large percentage of women previously sterile for long periods under therapy with pregnant mare serum became impregnated. This early clinical work has not been confirmed and it is now doubtful if the gonadotrope from pregnant mare serum, even in large doses, can induce ovulation in the woman on a practical clinical basis, since long continued therapy has been shown to form ovarian cysts rather than to cause ovulation. Application to humans of experimental work with animals other than mammals, is still more dubious on account of the species differences in physiologic processes.

Another cause of therapeutic disappointment is treating an organ that is incapable of response. For example, there is no use trying to stimulate the senescent ovary to secrete female sex hormone or to ovulate. When the ovary has run its course of sexual activity, it is finished and no amount of whipping by the over-active compensatory anterior pituitary or by administration of exogenous gonadotropes is of any avail. A tightly incarcerated undescended testis cannot be

persuaded to produce spermatozoa by any amount of gonadotropic hormone.

The physician must distinguish carefully between established and experimental therapy. A very few indications for hormone therapy are universally accepted. Among these are the use of estrogens in the menopause, the use of estrogens and androgens in proved hypogonadism in the female and male respectively, and the use of chorionic gonadotropin in selected cases of cryptorchidism. On the other hand, many uses of endocrines are still in the experimental stage and failure should not surprise the physician. Prominent among these experimental uses of hormones is the present vogue for treatment of cancer of the breast with androgens and in selected cases with estrogens, and the treatment of prostatic cancer with estrogens. Although excellent results have been reported in many cases, the percentage of failures is still high. Again, the value of hormones in treatment of various forms of alopecia is anything but established.

Recently, an adjunct to hormone therapy of sterility has appeared in the form of the enzyme hyaluronidase obtained from bull testes which is applied topically to the uterine cervix in order to make the cervical mucous plug more permeable to the spermatozoon and to dissolve the protective layer of follicular cells surrounding the ovum making it accessible to fusion with the spermatozoon.

A misuse of hormones in which the pharmacist sometimes participates is the practice of self medication. Occasionally, a pharmacist with a superficial knowledge of endocrine therapy gained largely from reading manufacturers' literature, is impelled to make recommendation to a customer concerning hormone therapy for menopause, impotence, etc. Nothing could be more dangerous because such apparently simple conditions as the menopause and impotence may be extremely complicated and involve, in the former case, surgical conditions, and in the latter psychiatric complications, requiring the best services of the best experts in these fields. But self medication by the laity, although of greater volume, is probably more innocuous than self medication by the physician. Routine correspondence between the American medical profession and endocrine manufacturers discloses a reprehensible, widespread practice among physicians of treating themselves with this or that hormone haphazardly without any real inquiry into the diagnosis. The old saying is certainly applicable in this case, the physician who treats

himself has a fool for a patient and a damned fool for a physician. The self-dosing physician is best served by the medical department of the pharmaceutical house and by the individual pharmacist by suggesting tactfully that he place himself under the care of one of his confreres especially qualified in the required field.

There will now be presented examples of personally observed misuse of the several hormones. Errors in the use of thyroid may be classified as sins of omission and sins of commission. Certainly thyroid is not used by physicians as frequently as it is indicated. There is a tendency, since the availability of the high powered, purified steroid hormones and gonadotropes to use them instead of the lowly, old fashioned thyroid. It should be kept in mind that thyroid is a stimulant to all the tissues of the body, including the glands of internal secretion, and that frequently better results are obtained by stimulating the deficient gland with small doses of thyroid than by supplying the deficient hormone in substitution therapy. Concurrent use of thyroid with other hormones potentiates their action. One of the leading specialists in sterility studies has stated that he has obtained more pregnancies in previously sterile women by the use of thyroid alone than by any other hormone. Another misuse of thyroid is its promiscuous employment as an obesity remedy. Federal law has brought this abuse largely under control in regulating the sale of obesity remedies containing thyroid, but formerly many deaths were caused by self medication with, and pharmacist-prescribed, preparations containing iodine for obesity, without periodic checkups of basal metabolic rate. Many cases of mild thyroid deficiency are overlooked and other glands are treated erroneously. In doubtful borderline cases of suspected thyroid deficiency, therapeutic test of thyroid should be made.

In the use of protein hormones, including the gonadotropes, a common error is to continue therapy for too long a period after they have lost their effectiveness due to production of anti-hormones or antibodies. Short courses of treatment with gonadotropes should be interspersed with rest periods of equal length. Chorionic gonadotropin should not be employed in very young boys in the treatment of cryptorchidism. This condition is corrected spontaneously in a great number of cases and boys should be permitted to go to or near puberty before meddling with hormones. If at that time the testicle has not descended, the hormone may be used in alternate periods of adminis-

tration and rest for a short time, but if unsuccessful, surgery should be resorted to.

Perhaps the most common misuse of posterior pituitary is its too early administration in the induction of labor with consequent rupture of the uterus.

Insulin is misused by the good natured physician when he prescribes it for the greedy diabetic who wants to indulge his appetite to any extent and balance the carbohydrate with injected insulin. The use of oral substitutes for insulin, Synthalin, Myrtillin, etc., has been controlled by the Federal Food, Drug and Cosmetic Act, but formerly considerable quantities of these ersatz substances were consumed inadvisably.

Epinephrine and epinephrine-like substances are widely misused, not only by the laity in self-medication, but also by the physician in p. r. n. prescriptions. These epinephrine-like substances are extremely potent for physiologic harm and should be carefully controlled. Adrenocortical hormones are misused when they are administered to patients with cardiac failure, increasing blood pressure in the cardiovascular system in which the heart is already embarrassed.

The hormones most misused are the sex hormones. For example, sterility in the male or the female is often treated solely by the administration of a sex hormone without proper examination of the patient's mate and without proper inquiry into all the facts concerned in the mating. Such hit or miss therapy is bound to fail. Estrogenic hormone is misused when it is given to a woman without previous thorough complete gynecologic examination. She may have fibroid uterine growth which would be stimulated by excessive estrogens. She may have uterine or mammary carcinoma in which estrogens would be definitely contraindicated. One such case was reported in which an eighteen year old girl who had never menstruated complained of pelvic pain and her physician, without any pelvic examination, gave her the usual one-two treatment with estrogens alternating with progesterone for a period of several months during which time the periodic pain was greatly increased. When the patient sought the advice of a gynecologist, pelvic examination disclosed the anomalous condition of absence of vagina. Bleeding during the painful months had been directly into the pelvic tissues in the same way that ectopic endometrial tissue in endometriosis

floods into the confined space causing pain. No female patient should be given hormones without a complete physical examination, including gynecologic.

Recent report in one of the medical journals described a case of endometriosis which had been controlled for a few months by the use of testosterone in inhibiting ovulation and therefore menstruation. This was followed by ovariectomy which, of course, controlled the endometriosis, but there followed the usual train of symptoms due to surgical menopause. These symptoms were treated by the administration of estrogens and, of course, the aberrant endometrial tissue became proliferative, secretory and exfoliated, bleeding into enclosed space causing the old pain. A basic knowledge of endocrinology would have indicated the use of testosterone in control of these menopausal symptoms because this hormone depresses the anterior pituitary just as do estrogens, but without causing bleeding of endometrial tissue.

Excessive dosages of estrogens in menopause frequently aggravate instead of controlling the symptoms.

A common error of administration of the female sex hormones, estrogens and progestins, is to administer them out of phase, that is, to disregard the alternate fortnightly periods of estrogenic and progestational activity. When estrogens and progestins are used concurrently, estrogens should be concentrated upon in the first fortnight, and progestins in the second fortnight of the menstrual period.

The general practitioner and other physicians sometimes assume that all abnormal manifestations after the age of forty-five are due to estrogen deficiency and accordingly use estrogens in their therapy. Among these symptoms which may in some instances be actually due to estrogen deficiency, but in many more cases are not, are arthritis, psychosis, hypertension and other natural changes due to age, such as graying of the hair, wrinkling of the skin, deposition of fat about the neck, girdle and hips. Occasionally, this arthritis or other condition may respond to estrogen therapy and it may then be assumed that the cause was estrogen deficiency.

Estrogens should not be employed in females with carcinoma, especially of the breast or pelvic organs or in females with definite family histories of carcinoma. Androgens should not be employed in treatment of males with carcinoma. Promiscuous, injudicious progesterone therapy in uterine bleeding without adequate gynecologic

examination and endometrial biopsy is criminal. Uterine bleeding may be due to malignancy in which no hormone is of use. This is one particularly dangerous misuse of hormones in which a neglect of other conventional, necessitous treatment in favor of hormones alone leads to irreparable damage. The delay in proper diagnosis alone is a matter of criminal neglect.

The use of massive doses of estrogens in young girls leads to undesirable sexual precocity, not only in bodily development, but also in the psychic patterns. Too early use of androgens in the male leads to the same result.

When the value of progesterone in preventing abortion became known, it was thought that we have here an unqualified blessing, but Corner and others soon showed that nature knows better than the physician, because a greater proportion of abnormal fetuses was found among those aborted than among those going to term. The physician must therefore give progesterone to prevent abortion with the mental reservation that he may be saving an undesirable fetus that might be born a monster.

In the early days of sex endocrinology a sharp line of distinction was drawn between male and female sex hormones, each being used only in its own sex. Now, however, this specificity has been found to be over-rated, and androgens are used in the female and estrogens in the male under proper circumstances. When androgens are used in the female, however, the total monthly dosage of testosterone should be limited to about 300 milligrams, or there will result evidence of virilization, as oiliness of the skin and hair (even resulting in acne), male distribution of the hair, lowering of the pitch of the voice and hypertrophy of the clitoris. But occasional use of androgens in the female as for the control of otherwise intractable dysmenorrhea is without such danger. However, dysmenorrhea is a complicated condition and sometimes is not in any way related to hormone deficiency. The use therefore of progesterone or testosterone without thorough gynecologic study is inexcusable.

Enuresis, when not due to anataomical causes, such as phimosis, may be controlled by testosterone. A burly Chicago police officer, 33 years of age, who had wet the bed every night of his life, after a few injections of testosterone, twenty-five milligrams, was permanently cured.

Too early use of androgens in excessive doses theoretically may depress the pituitary sufficiently to close the epiphyses prematurely causing dwarfism. However, studies by McCullagh and others have shown that practically this is very unlikely to happen.

Many studies of the value of hormones in homosexuality have resulted in a confusion of reports. For example, one investigator used testosterone in treating male homosexuals in a penal institution where there was no opportunity for normal sexual outlet and reported that testosterone aggravated the homosexual condition. This would seem to be an unfair and improperly controlled study.

Testosterone therapy is not a substitute for prostatectomy in benign prostatic hypertrophy, but it does bring relief from the more intense urinary symptoms by giving better tone to the bladder muscles, just as it does to the skeletal muscles. Testosterone is misused, however, when it is employed in place of a plainly indicated prostatectomy. Some urologists use testosterone pre- and postoperatively for its effect on bladder tone.

Just as not all symptoms in the woman past forty-five are due to female sex hormone deficiency, so not all the symptoms in the male at this age are due to male sex hormone deficiency. Yet, quite a sales patter has been built around the idea that there is a definite male climacteric with symptoms of loss of concentration, increased emotionalism, impotence, insomnia, nervousness, tremor and indefinite gastrointestinal symptoms due to lack of male sex hormone. The physician who employs testosterone in the hope of curing all the miscellaneous pathologic conditions in the male, age fifty, is doomed to disappointment. When treating impotence with androgens the mistake is sometimes made of stimulating the patient beyond his cardiovascular capacity, resulting in sudden death. Mistaking prostatic cancer for benign prostatic hypertrophy and administering androgens lead to exacerbation of the cancerous growth and its dissemination through metastases. The current endocrine therapy of prostatic cancer is the administration of estrogenic hormones as ethinyl estradiol, stilbestrol, etc.

In considering the inhibition of lactation, the physician is usually guided by the wish of the patient as to whether she will or will not nurse her child. One important further consideration should always be taken into account, namely, the possibility of transmission of cancer susceptibility to the child through the milk factor. Dr. Hammett of

The Lankenau Hospital group has recently called attention to the undesirability of mothers of cancerous family history nursing their infants. When it is decided that lactation is to be inhibited, one of several hormones may be used. Estrogenic hormone is probably the most physiologic substance to be employed, although androgens are also useful. Recently work with ethinyl estradiol shows it to be the hormone of choice for this purpose. However, the mother should be persuaded to nurse the child unless there is some better reason for not doing so than that she wants to return to her social duties.

In summary, the manufacturer, the pharmacist and the physician can all contribute toward a discontinuance of the several misuses of hormones. The manufacturer should desist from distributing non-hormone preparations designated as endocrine, as well as inactive dosage forms of the true hormones. Units of all pure substances should be dropped. Polyglandular preparations should be avoided. Hormone cosmetics should be shunned. The pharmacist should discourage self-medication, especially by physicians, and should serve as a source of information from which the too busy physician can obtain reliable evaluations of the host of hormone preparations continuously flooding the market. The physician, in turn, if not equipped for complete endocrine diagnosis and if not adequately experienced, should limit his hormone therapy to the generally accepted and established indications. He should leave the still experimental uses of hormones to his more experienced and better equipped confreres. In meddling with these highly active substances, he may upset irreparably the delicate interbalance among the glands of internal secretion, or, still worse, by fixing his attention on the ineffectual administration of hormones, he may overlook the real diagnosis and neglect the conventional, time-honored procedures of therapy, permitting the pathologic process to progress beyond the point of correction. And this pathologic process is not infrequently cancer.

THE DETOXICATION OF PENTAVALENT ARSENICALS

By Gustav J. Martin *

THE work of Sandground (1, 2, 3) on the detoxication of pentavalent arsenicals by p-aminobenzoic acid raised immediately the question of the specificity of such a reaction. Sandground states that it is the property of certain other unrelated compounds (26). For several years (4, 5, 6, 7) we have been studying the effects of various agents which behave in enzyme systems as p-aminobenzoic acid does. There is little structural specificity in these systems: some chemicals act in protecting adrenaline from oxidation (7) because of a similarity of structure, others act because they inhibit enzyme systems which are involved in the catalytic destruction of these agents. As it seemed probable that Sandground was dealing with chemicals capable of influencing oxidation and reduction reactions and as p-aminobenzoic acid was an effective chemical in many of the systems studied by us, it was decided to try some of these in the detoxication of pentavalent arsenicals. As our sole interest lay in an investigation of the mode of action of certain chemicals in detoxifying pentavalent arsenicals no chemotherapeutic studies were undertaken.

Procedure

Oral administration of arsenical was used throughout. Acetarsone (stovarsol, acetylaminohydroxyphenylarsonic acid) and arsanilic acid (atoxyl) were the pentavalent arsenicals used. The only variables in the study were dosages and detoxifying chemical agents. Chemicals known from experience (6, 7) to impede or facilitate the oxidation of adrenaline in a tyrosinase system were used. These agents might generally be regarded as retarders of metabolism. They actually slow down certain metabolic processes. Included among these agents are sulfanilamide, p-aminobenzoic acid, thiourea, S-methylisothiourea, thiouracil, catechol, thiobarbituric acid, thioacetamide, potassium thiocyanate, tyrosine thiohydantoin, sodium salicylate. Urea peroxide and sodium bisulfite were tested for the effect of an oxidizing and a reducing agent of the commoner variety.

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Tables I and II indicate the reduction in toxicity. Mice were used throughout. They were maintained before use on regular stock mouse diet.

TABLE I

DETOXICATION OF ARSANILIC ACID 1.8 mg./g. ARSANILIC ACID (LD 100) SUBCUTANEOUSLY

100 Mice per Set

	Compound	Dosage	% Deaths
1	Aspartic Acid	2.5	40%
2	Alanine	2.0	60%
3	Arginine	2.0	N
4	Acetic Acid	2.0	N
5	o-Aminobenzoic Acid	0.5	22%
6	m-Aminobenzoic Acid	1.0	43%
7	p-Aminobenzoic Acid	2.5	51%
8	Ascorbic Acid	2.5	62%
9	Adenine	2.0	N
10	p-Aminophenylacetic Acid	1.0	45%
11	Atophan	0.25	67%
12	B-Alanine	1.0	N
13	NH_4Cl	2.0	N
14	Benzoic Acid	1.0	75%
15	Cystine	2.0	N
16	Cysteine	1.0	N
17	Citric Acid	1.0	64%
18	Catechol	0.1	N
19	Ephedrine	0.1	N
20	Glycine	2.0	50%
21	Glutamic Acid	2.0	N
22	Glutathione	2.0	N
23	Glucurone	2.0	N
24	Glucose	2.0	N
25	Histidine	2.0	N
26	Hesperidin	3.0	75%
27	p-Hydroxybenzoic Acid	0.25	86%
28	Isoleucine	2.0	67%
29	Isothiourea	0.25	N

30	Isoascorbic Acid	1.0	68%
31	Inositol	0.5	N
32	Leucine	2.0	N
33	Lysine	2.0	N
34	Lactic Acid	2.0	N
35	Liver	2.0	N
36	Methionine	2.5	61%
37	Nicotinamide	0.5	N
38	Phenylalanine	2.0	26%
39	Proline	2.0	N
40	Pyruvic	1.0	N
41	Pepticase	2.0	N
42	Pyridoxin	0.5	N
43	Pantothenic	0.5	N
44	Riboflavin	0.5	N
45	Serine	2.0	45%
46	Succinic	2.0	N
47	Sulfanilamide	1.0	90%
48	Sodium Acetate	2.0	N
49	Sodium Bisulfite	0.25	N
50	Sodium Salicylate	0.2	91%
51	Sodium Bicarbonate	2.0	N
52	Saccharin	1.0	86%
53	Sulfanilic Acid	2.0	83%
54	Tyrosine	2.5	79%
55	Threonine	2.5	45%
56	Tryptophan	2.0	80%
57	Thiocyanate	0.25	66%
58	Tyrosine Thiohydantoin	0.5	N
59	Thioacetamide	0.2	N
60	Thiourea	0.5	N
61	Thiouracil	0.2	N
62	Thiamin	0.5	65%
63	Valine	2.0	70%
64	Urea Peroxide	0.25	N

N=No effect

TABLE II

DETOXICATION OF ACETARSONE 4.0 g./KG. ACETARSONE SUBCUTANEOUSLY

50 Mice per Set

	Compound	Dosage Gm./Kg.	Average Deaths
1	Na PAB	2.5	37%
2	S-Methylisothourea	0.15	43%
3	Thiourea	0.5.	100+%
4	Thiouracil	0.2	100+%
5	Catechol	0.1	100+%
6	Thiobarbituric Acid	0.5	56%
7	Thioacetamide	0.2	100+%
8	K Thiocyanate	0.25	50%
9	Tyrosine Thiohydantoin	0.5	50%
10	Sulfanilamide	1.0	76%
11	Na Salicylate	0.2	50%
12	Benzoic Acid	1.0	0%
13	Urea Peroxide	0.25	100%
14	Na Bisulfite	0.25	100%
15	Tyrosine	2.5	100%
16	Threonine	2.5	70%
17	Ascorbic Acid	2.5	73%
18	Methionine	2.5	62%
19	Aspartic Acid	2.5	26%
20	Isothiourea	0.25	100+%

Results

Thyroxine administered with the p-aminobenzoic acid nullifies to a considerable extent its ability to detoxify pentavalent arsenical agents. Table III shows the results of experimentation of this type.

TABLE III

THE EFFECT OF THYROXINE ON THE p-AMINOBENZOIC ACID DETOXICATION OF STOVARSOL

100 Mice per Set. Percentage Deaths

Stovarsol 3 g./kg. Subcutaneous	Stovarsol plus PAB Oral 2g./kg.	Stovarsol plus PAB plus thyroxine 200 ug.	Thyroxine 200 ug. orally plus Stovarsol
65%	10%	100%	25%

The p-aminobenzoic acid (3 g./kg.) and the thyroxine (200 μg.) were given orally 1½ hours before the Stovarsol (3 g./kg.) was given subcutaneously.

TABLE IV

EFFECT OF THYROXINE AND p-AMINOBENZOIC ACID ON TOXICITY OF ARSANILIC ACID (MLD 50+ = 1.6 mg./gram)
(Subcutaneous)

20 Mice in Each Set

Thyroxine and p-Aminobenzoic Acid Given Orally

	Arsanilic Acid 1.6 mg./gram	Arsanilic Acid 1.6 mg./gram Paba 2 mg./gram	Arsanilic Acid 1.6 mg./gram Paba 2 mg./gram Thyroxine 0.20 ug./gram	Arsanilic Acid 1.6 mg./gram Thyroxine 0.20 ug./gram
1	70%	40%	50%	100%
2	80%	45%	75%	70%
3	85%	60%	100%	100%
4	90%	70%	100%	90%
5	100%	70%	90%	100%
6	88%	78%	84%	84%
7	76%	8%	12%	20%
8	80%	60%	44%	96%
Average	84%	63%	70%	84%

Discussion

The simultaneous administration of thyroxine and p-aminobenzoic acid brings about a condition in which there is no inhibition of the toxicity of the arsenical. This proves that PABA acts by decreasing tissue metabolism, a direct result of thyroxine inhibition.

Tolerance to some types of drugs is in some manner related to thyroid function. According to Benedict et al.(8), patients with myxedema tolerate morphine poorly. Lerman (9) feels that such patients tolerate digitalis poorly and other sedative drugs extremely well. These findings may be attributed to the metabolic action of thyroid. In the same category is the acetonitrile reaction of Hunt (10) in which the increased resistance of mice to acetonitrile resulting from the feeding of thyroid is demonstrated. Increased resistance of mice to fluorine toxicity in animals receiving thyroid was demonstrated by Wilson and his group (11). It may be that generalized

alterations in metabolic rate, which would result in increase or decrease in the rate of oxidation or reduction of certain drugs and chemicals, is the determining factor in toxicity variations. This would probably mean that patients with fever would be more susceptible to some drugs and less susceptible to others. One concrete example of the manner in which thyroxine specifically alters metabolism is the demonstration of Klein (12) that the administration of thyroxine produced an increase in the activity of d-amino acid oxidase in the liver. This enzyme is composed of a specific protein and a flavin adenine dinucleotide; the increase in activity of the oxidase is probably due to an increase in the concentration of its protein component and not to change in the nature or concentration of prosthetic radical of the enzyme.

It is generally recognized that in many processes of detoxication, oxidation or reduction precede the coupling reaction. In fact, oxidation and reduction may be the only process involved in the detoxication. This facilitation of physiological oxidation or reduction is not of such a nature that detoxication necessarily results. In fact, some of the processes generally spoken of as detoxication reaction are at times found to result in increased toxicity of the chemical altered. Thus the acetylation of sulfanilamide produces a compound which is more toxic than is the parent chemical (13). A general recognition of the part played by detoxication processes in drug sensitivity reactions would doubtless clarify many incompatibilities. Facilitation or inhibition of the alteration of molecules supplied to the body as drugs could become a process useful in general medicine as it is certain that in many instances alteration in those molecules results in decreased therapeutic value.

As stated by Astwood (14), the chemicals promoting hypertrophied thyroids with hypothyroidism function in two general ways; p-aminobenzoic acid because of its similarity of structure with thyroxine, thiourea because it is a specific inhibitor of enzymes involved in the formation of thyroxine.

Generally but with exceptions, the chemicals found effective in decreasing the toxicity of pentavalent arsenicals are those which have been found to possess the following characteristics:

1. Pseudopotentiation of insulin (15);

2. production of hypertrophied thyroids with hypothyroidism (14, 16, 17, 18, 19);

3. protection against the toxic action of thyroxine (20);

4. protection of adrenaline against oxidation by tyrosinase (7);

5. clinical effectiveness against hyperthyroidism (21);

6. inhibition of vitamin synthesis in the intestinal tract (22).

As the list of effects of the administration of these chemical agents grows it becomes more and more apparent that they will be effective in any reaction in which a generalized metabolic retardation is indicated. The list of these agents is not complete in any sense. Detail of the mechanism of their action is not complete; some function because of structural similarity to enzyme substrates, some function through direct inhibition of the enzymes themselves.

It is a unique characteristic of this process of detoxication that high dosages are necessary in order for paba to afford protection. These doses are of the same order as those necessary to bring about the other known biological effects of paba (15, 16, 17, 20). This fact does not preclude the arsenoxide theory; it merely involves several additional systems. The timing interval for effectiveness of paba in detoxifying pentavalent arsenicals (2) is much the same as that noted in attempts to potentiate the action of insulin by these chemicals (20). Paba given thirty minutes after the pentavalent arsenical does not materially aid in its detoxication: this is the time interval for loss of effectiveness in the pseudo-potentiation of insulin by paba.

p-Aminobenzoic acid possesses the ability to inhibit the action of atoxyl against E. coli (23). This fact may make it unfavorable for use with arsenicals. On the other hand, sulfanilamide and the isothioureas do not possess this characteristic, and yet they are effective in the detoxication of pentavalent arsenicals. The trypanocidal action of pentavalent arsenicals is markedly increased as is their toxicity by treatment with thio compounds which result in the formation of arsenoxides (24). The detoxication mechanism must however be motivated via reduction of the arsenic or it could be by oxidation of the amino group to a hydroxylamino radical. This mechanism is improbable as the formation of some oxidation products of the nature of hydroxylamino compounds from sulfanilamide is probable and p-aminobenzoic acid does not detoxify the sulfonamides. Further p-aminobenzoic acid does not detoxify trivalent arsenicals which again speaks for the arsenoxide theory. Support of the arsenoxides

formation theory has resulted from the demonstration by Peters (25) that paba does not detoxify mapharsen (m-amino-p-hydroxyphenylarsenoxide).

Under our experimental conditions, the most powerful detoxifying agents were threonine, aspartic acid and serine. These amino acids are effective against two lethal doses of arsanilic acid. Ascorbic acid is equally as potent as p-aminobenzoic acid. Against one lethal dose of arsanilic acid it is as potent as threonine but against two lethal doses it was not effective; whereas threonine, aspartic acid and serine were highly effective saving the lives of between 20 and 60% of the animals. Methionine was not as effective as the above mentioned agents. It is to be noted that the dosages used were equivalent to the dosages of the arsenical used. Table I indicates the relative order of efficiency of the various agents.

Table V shows results obtained in an attempt to secure detoxicant potentiation. Subsequent trials have disclosed that these agents do not potentiate one another.

TABLE V

EFFECTIVENESS OF COMBINATIONS OF DETOXIFYING AGENTS IN DETOXICATION OF ARSANILIC ACID

All Groups 20 Mice Each

All Mice Received LD 100 of Arsanilic Acid

Compound Combination	Dosage mg./gm.	Percentage Deaths	Order of Efficiency
Hesperidin and Ascorbic acid	2½ ea.	52%	5
Hesperidin, Ascorbic acid and Paba	1¼ ea.	40%	4
Threonine and Paba	1¼ ea.	40%	4
Ascorbic acid and Paba	2½ ea.	40%	4
Cysteine and Ascorbic acid	1¼ ea.	35%	3
Serine and Aspartic acid	2½ ea.	10%	1
Serine, Aspartic acid and Threonine	1¼ ea.	25%	2
Serine and Ascorbic acid	2½ ea.	40%	4

Hesperidin may under certain conditions aid the activity of ascorbic acid, but generally it may be stated that potentiation does not occur. This point is of importance as a factor in consideration of the problem of the mode of action. If some chemicals act by structural

displacement of the arsenical and others act by the inhibition of oxidation-reduction mechanism, then potentiation should occur. It is an extremely lengthy process to try all combinations of some forty or fifty different single chemicals, each of which is effective. Therefore we do not propose to state conclusively that the various agents do not potentiate one another. It can be stated that the following combinations show no potentiations: hesperidin and ascorbic; hesperidin, ascorbic and p-aminobenzoic acid; threonine and paba; ascorbic and paba; cysteine and ascorbic; serine and aspartic; serine and ascorbic acid; and serine, aspartic acid and threonine.

As to the question of the general mechanism underlying this action, it is suggested in spite of the failure to demonstrate potentiation that there are at least three or four different mechanisms of activity. One of these might well be structural displacement. The p-aminobenzoic acid and arsanilic acid structures are decidedly similar. Paba nullifies the anti-bacterial action of arsanilic acid. A second general mechanism might well be oxidation and reduction. The agent, for example ascorbic acid might act by prevention of the conversion of the pentavalent arsenical to the arsenoxide form. A third mechanism is protection of the liver as found in the activity of methionine in detoxifying arsenicals. A fourth is action on the capillaries, protecting the capillary from disruption as seen with hesperidin and perhaps as a secondary effect of ascorbic acid. From a general consideration of processes of detoxication it is not to be expected that one explanation could be offered for the activities of the various agents.

The point of structural similarity can be discarded entirely. There is no similarity between structure of p-aminobenzoic acid, ascorbic acid, hesperidin, methionine, aspartic acid and serine. A thorough examination of these molecules discloses no point of similarity in structure.

Summary

p-Aminobenzoic acid and certain other chemicals detoxify pentavalent arsenicals by virtue of their ability to inhibit the formation or action of thyroxine which results in a generalized decrease in tissue metabolism with consequent inhibited arsenoxide formation. This is not a specific mechanism and should apply to any drug which is more toxic in its oxidized or reduced form.

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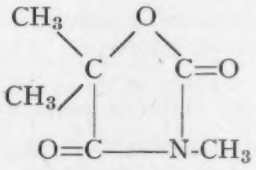
SELECTED ABSTRACTS

Aplastic Anemia and Agranulocytosis Following Tridione: A Fatal Case. R. P. Mackay and W. K. Gottstein. *J. A. M. A. 132,* 13 (1946). The authors report a case in which death resulted from acute aplastic anemia, agranulocytosis and thrombocytopenia, with extensive hemorrhages throughout the body, following the administration of Tridione (Abbott), together with phenobarbital, over a period of ten months.

Tridione, which is 3, 5, 5-trimethyloxazolidine-2, 4-dione, has been used as an anticonvulsant in the treatment of petit mal and psychomotor seizures. Its structure is as follows:



Within the clinical experience of one of the authors, as well as of other investigators who have published their observations, the drug has favorably influenced petit mal, especially in children. A side effect generally noted has been hemeralopia (a blurring of vision in bright light); nausea, skin eruptions, lightheadedness and drowsiness occasionally occur.

In the case reported, the patient had been treated with phenobarbital almost constantly for nineteen years; at times bromides and diphenylhydantoin sodium had also been used. When Tridione therapy was instituted, the drug was given in 0.3 gm. doses three times daily, in addition to 0.25 gm. of phenobarbital daily. During the course of treatment the frequency of dosage of Tridione was varied somewhat, but was never more than six 0.3 gm. doses daily, with 60 mg. of phenobarbital per dose.

The course of the final illness is described in detail, accompanied by clinical charts. The authors present recommendations to govern the use of the drug. Contraindications include severe anemia of any type, all hemorrhagic tendencies and all previous or present deficiencies of the granulocytic series.

Streptomycin in the Treatment of Infections: A Report of One Thousand Cases. The Committee on Chemotherapeutics and Other Agents, National Research Council: C. S. Keefer *et al. J. A. M. A. 132,* 4 (1946). This report presents the observations of a group of 55 clinical investigators accredited to the Committee under the chairmanship of Dr. Keefer, and of numerous other physicians who cooperated with the Committee.

The cases selected for clinical trial of streptomycin were those judged most likely to be benefited by it and those which were resistant to penicillin and the sulfonamides.

For systemic treatment the intramuscular route is the one of choice. Other modes of administration for the drug include subcutaneous, intrathecal, intraperitoneal, and intrapleural injections; it may be given orally for its bacteriostatic effect in the gastrointestinal tract, and it may be applied topically. The drug has also been given by the inhalation of a spray in the treatment of bronchopulmonary infections.

The report presents a brief discussion of each of the groups of infections, describing the dosage used, the route of administration, the length of the course of treatment, and the results.

The following table summarizes the results:

	Number of Patients	Recovered	Results: Improved	Results: No Effect	Died
Urinary tract infections	409	171	145	84	9
H. influenzae meningitis	100	66	14	3	17
Bacteremia	91	49	12	4	26
Tularemia	67	63	..	3	1
Pulmonary infections	44	15	14	7	8
Brucellosis	45	..	30	15	..
Typhoid	51	..	51	..	..
Salmonella	26	10	2	6	8
Peritonitis	53	36	3	2	12
Meningitis due to gram-negative organisms other than H. influenzae	14	5	5	..	4
Shigella dysenteries	2	2	..	..	..
Miscellaneous infections	98	36	29	30	3
Totals	1000	453	305	154	88

Kemithal: A New Hypnotic. R. R. Macintosh and R. D. Scott. *Lancet 1, 767* (1946); through *Pharm. J. 103,* 136 (1946). Kemithal is 5-cyclohexanyl-5-allyl-2-thiobarbituric acid. It is insoluble in water, but its sodium salt is water-soluble (1:5), and the solution is stable for four to five hours. The pH of a 10 per cent solution is 11.2; the corresponding value for hexobarbitone is 11.5 and for thiopentone 10.6.

In clinical trials on 400 patients Kemithal was administered to fifty as the sole anesthetic, and as an induction anesthetic in the remaining cases. Its potency was about one-half that of thiopentone. The dosage was from 0.5 to 6.3 gm., usually as a 10 per cent solution; for a healthy adult undergoing appendectomy, the dose was 3 to 4 gm.

Nausea and vomiting were rarely noted, and the tendency to postoperative vomiting appeared to be less than with other barbiturates.

Nicotinamide Deficiency After Oral Administration of Penicillin. P. Ellinger and F. M. Shattock. *Brit. Med. J.* No. 4477, 611 (1946). The oral administration of penicillin in the treatment of a case of pharyngitis resulted in darkening of the tongue, in addition to the usual symptoms of nicotinamide deficiency. The drug was administered over a period of five days; 15 tablets containing 500 units each were placed on the dorsum of the tongue and allowed to dissolve. In addition, the patient received orally penicillin in saline solution (500 units/ml.).

The symptoms noted at the end of five days were a dark slaty color of the tongue, lassitude, inability to concentrate on mental work, subjective sensory changes in both legs, and the development of a dry, coarse, inelastic condition of the skin of the forearms and back of the hands.

Upon discontinuance of penicillin and the administration of nicotinic acid in doses of 200 mg. three times daily for three days, the subjective symptoms were relieved. Several additional days were required for the condition of the tongue and skin to return to normal.

A report is also presented of further investigations made on the same patient of the effect of oral penicillin in decreasing the daily urinary output of nicotinamide methochloride.

It is recommended that the nicotinamide status of patients under treatment with oral penicillin should be watched, and that if necessary nicotinamide should be administered parenterally.

Other investigators have previously reported nicotinamide deficiency symptoms after the oral administration of succinylsulfathiazole or sulfaguanidine, and of "black tongue" after sulfadiazine or penicillin by the same route.

Bases for Sterilized Penicillin Cream. J. B. Hough and A. H. Pryce. *Pharm. J. 103,* 102 (1946). Sterilized penicillin cream prepared according to the B. P. formula was found to be alkaline prior to autoclaving, but to become somewhat acid thereafter. The authors therefore studied the effect of adding a buffer in an amount corresponding approximately to 1 per cent of the Lanette wax SX used. The buffer was a mixture of two parts of boric acid and one part of borax.

Three pairs of products were studied, representing the B. P. formula and two modifications of it; one of each pair contained no buffer and served as a control. Product *A* (B. P. formula) contained Lanette wax SX 7 gm., hard paraffin 5 gm., liquid paraffin 41 gm., and sterilized water 37 mils. The pH was 9.2 before autoclaving, and 6.6 thereafter. Product *B,* which represented *A* plus 0.1 gm. of buffer, had a pH of 8.8 before autoclaving, and 7.4 thereafter.

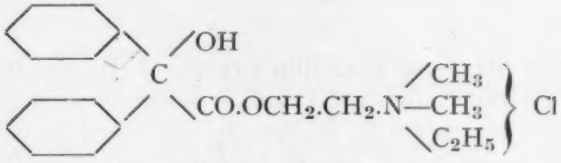
Product *C* contained 12 gm. of Lanette wax SX, but no hard paraffin; its pH was 9.2 before autoclaving, and 6.0 thereafter. Product *D* (*C* plus 0.1 gm. of buffer) had a pH of 8.8 before autoclaving, and 7.0 thereafter.

In product *E* the B. P. formula was changed by reducing the amount of liquid paraffin to 31 gm. and increasing the sterilized water content to 47 mils. The pH was 9.4 before autoclaving, and 5.0 thereafter. Product *F* (*E* plus 0.1 gm. of buffer) had a pH of 8.6 before autoclaving, and 7.0 thereafter.

Only in the case of *C* was a cracking of the emulsion observed after autoclaving. The authors conclude that the B. P. formula yields a satisfactory emulsion of good consistency, but recommend the addition of a buffer.

Anesthesia and Analgesia: Highlights of Recent Work. F. J Dyer. *Pharm. J. 103,* 107 (1946). The author presents material excerpted from a number of papers published in an "Anaesthesia Centenary" number of *Brit. Med. Bull. 4,* 2 (1946).

Atropine Substitutes. During the war, research on synthetic mydriatics led to the development of benzilyloxyethyl dimethylethyl ammonium chloride, for which the name "lachesine" has been proposed. Its structure is as follows:



Pharmacological investigations were performed upon lachesine and twelve other benzilylcholine derivatives, with atropine as the reference standard with a value of 100. In these experiments the following results were obtained for lachesine: (1) in antagonizing the flow of saliva experimentally induced by pilocarpine and carbamylcholine in the cat, 258 ± 38; (2) in modifying the blood-pressure of the cat, 182; (3) in producing mydriasis in the pupils of mice, 104.4.

Toxicity studies on lachesine revealed that its LD_{50} in mg. per 20 gm. body weight of mouse was 0.8 intraperitoneally, 3.2 subcutaneously, and 20.0 orally. For atropine sulfate these values were 6.4, 15.0, and 15.0, respectively.

Clinical trials of lachesine indicate that it holds promise in ophthalmic surgery as a short-acting mydriatic and cycloplegic and for the treatment of patients who are allergic to the belladonna alkaloids.

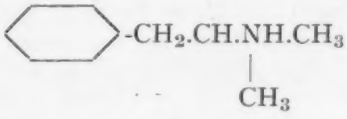
Morphine Substitutes. Over a period of many years numerous synthetic substances based upon the phenanthrene, dibenzofuran and carbazol nucleus have been prepared. Of those which had high analgesic/narcotic and low emetic/toxic effects, only methyl dihydromorphinone survived clinical trial.

Since 1944 Dodds, Lawson and Williams have prepared a series of 17 derivatives of diphenylethylamine; five of these compounds received clinical trial. Two of these appeared promising: αβ-diphenyl-

ethylamine and β-hydroxy-αβ-diphenylethylamine. The latter, administered in 200 mg. doses every four hours, gave complete relief of pain in 14 cases without undesirable side- or after-effects. Its use is limited to pain associated with nerve-pressure (e. g., carcinomata).

Asepsis in Spinal Anesthesia. Garrod believes that many cases of meningitis following spinal anesthesia are due to infections caused by Gram-negative bacilli of types found in the water used for rinsing syringes and needles. He advocates that all apparatus used for lumbar puncture should be sterilized by dry heat and that special precautions be taken in regard to the sterile distilled water used.

Maintenance of Blood Pressure. Studies have been made by Burn of the efficacy of several compounds as peripherally-acting pressor drugs in restoring the blood pressure following the administration of a spinal anesthetic. The action of ephedrine, neosynephrine, pholedrine, phedracin, and methedrine (pervitin) were investigated on the cat heart, following the depression of the blood pressure by the injection of a large dose of pentobarbitone. Of these compounds, ephedrine and methedrine were the drugs found most satisfactory. Methedrine has the structure:



Curare. Hewer regards it as probable that the main action of pure curare is to neutralize the acetylcholine mechanism of transmission of nerve impulses at the myoneural junction. The drug is available as "Intocostrin" Squibb and "Curarine Chloride" Burroughs Wellcome.

It is stated that perfect muscular relaxation during light anesthesia can be obtained by the use of curare. Hewer prefers endotracheal anesthesia, because if bronchospasm occurs it can be readily controlled. Prostigmine may be administered as the physiological antidote.

BOOK REVIEWS

Lessons in Pharmaceutical Latin and Prescription Writing and Interpretation. By Hugh C. Muldoon, D. Sc., Dean, School of Pharmacy, Duquesne University. Fourth Edition. John Wiley & Sons, Inc., New York, 1946. vii + 256 pages, including index. Price: $2.50.

The fourth edition of Dean Muldoon's well-known text will be welcomed by teachers of pharmaceutical Latin, since the book has been revised to include the terminology of the forthcoming U. S. P. XIII and N. F. VIII. The Latin-English vocabulary contains, e. g., the new terms *suraminum, progesteronum, penicillinum, sulfamerazinum,* and others. It may be mentioned, however, that some new words have been omitted, e. g., *methacholina, iodopyrinum* and *arachis.*

The arrangement of the text is much the same as that used in the third edition. A new feature is the inclusion in Chapter XIX of the International Protocol titles of certain preparations, with the Latin titles of the corresponding U. S. P. or N. F. products. For the first time in this text the vocabularies in the first seven chapters are so arranged that the words are grouped according to the parts of speech.

The translation exercises have been extensively revised and include a number of titles selected from the N. N. R. and P. R. B., as well as the U. S. P. and N. F. Most of the illustrative prescriptions are new; a number of these were obtained from the files of two leading professional pharmacies in Pittsburgh.

New material has been introduced into the optional exercises provided at the end of each chapter. The questions are intended to stimulate the student's thought; e. g., the student may be asked to give a Latin cognate for each of several English words, to comment on one of the illustrative prescriptions on the preceding page, or to answer a question involving Latin grammar.

The list of abbreviated terms and phrases contained in the Appendix has been increased to sixteen pages in the present edition.

The text appears to be nearly free of errors; a brief examination revealed only two: on page 87, under a discussion of Homeopathic Prescriptions, "3x" should read "3X"; on page 199, "anhydroxyprogesteronum" and "anhydroxyprogesterone" should read "anhydrohydroxyprogesteronum" and "anhydrohydroxyprogesterone," respectively.

Although there may well be a division of thought among teachers of pharmaceutical Latin as to the approach to the new official English titles, to the reviewer it seems preferable to acquaint the student from the outset that the word order of the English titles will be considerably different from that seen heretofore. Dean Muldoon's book would possess added usefulness if it contained a list of typical official titles of the U. S. P. XIII and N. F. VIII, both in English and Latin, together with their synonyms. It has been the policy of the reviewer in teaching this course to introduce the more important synonyms, both official and non-official, after the student has mastered the fundamentals of Latin grammar. Thus, given the synonym, the student should be able to state both the official English and Latin titles of a drug or preparation.

A. A. DODGE.

Extractives from Northeastern Woods. Bulletin No. 9. Northeastern Wood Utilization Council, P. O. Box 1577, New Haven 6, Conn., 1946. Paper, 62 pages. Price: $1.00.

The advent of both World Wars, especially II, focussed attention upon the shortages which existed in the essential oil field in this country. Out of this need, as Percy C. Magnus points out in an introductory statement, came the realization that ample natural sources of many raw materials exist in the United States. The need for continued research in this field is certainly indicated.

A review of the literature on extractives which have been obtained from the trees and shrubs of the American Northeast is presented by Robert S. Aries, Director of the Northeastern Wood Utilization Council. The products which are actually marketed are briefly discussed; included under this heading are maple syrup, sweet birch oil, juniper oil, sassafras oil, cedarwood oil, hemlock bark (for its tannin content), Canada turpentine, and witch-hazel water.

Potential sources of marketable extractives from the northeastern woods are also indicated.

The chemical composition, percentages of constituents soluble in ether, alcohol, and water, and the uses of numerous northeastern extractives and woods are presented in tabular form.

Commercial production of essential oils in the Northeast is discussed by Arthur H. Downey, Technical Director of Magnus, Mabee & Reynard, Inc.

Data on the yields of essential oils, the necessary apparatus, capital cost and operating budget for a small distillation plant are supplied by Mr. Aries.

The bulletin includes a bibliography of references on the conifer leaf industry, a tabulation of recent essential oil imports into the United States, and a list of 149 American firms producing or dealing in essential oils.

The booklet should be both helpful and challenging to all persons interested in the production and chemistry of plant products from the American Northeast.

A. A. Dodge

Hayfever Plants. By Roger P. Wodehouse, Ph. D. Chronica Botanica Co., Waltham, Mass. G. E. Stechert and Company, New York, N. Y. $4.75.

This book brings together very nearly all of the botany that it is desirable to know in order to gain a clear understanding of the role that plants and their pollens play as causes of the allergies, hayfever and asthma. It could as well be called the Botany of Hayfever or the Botany of Allergy, though it is not intended to reach much beyond the botanical aspects of hayfever and asthma.

This volume was written largely in response to questions that have come to the author from members of the medical profession, from plant scientists and from sufferers of hayfever.

In order to be familiar with the botanical facts concerning these hayfever plants a thorough mastery of the complicated subject of plant taxonomy is necessary. In addition one must have a working knowledge of the morphology of plants, their relationships, their ecology, their geography and the morphology of their pollen grains. The author in this volume presents essentials of the various dis-

ciplines of botany brought together with the elimination of all materials not bearing directly on the study of hayfever and asthma. The book tells which plants cause hayfever, with special attention to the numerous and confusing vernacular and Latin names by which they have been designated in medical literature and elsewhere. It tells why certain plants cause hayfever while others, perhaps similar and closely related, do not. Those which do may be recognized by the structure of their flowers and inflorescences. An explanation is given as to why hayfever plants grow in certain places and are excluded from others, and the effect of the impact of civilization on our environment in their distribution. The author also explains which plants are the primary and which the secondary causes of hayfever and their seasons of activity in the various floristic areas throughout North America, and tells how the grains of pollen are caught from the air, identified and number estimated.

M. O. H.

Free Medical Care. Compiled by Clarence A. Peters. 378 pages incl. references, 1946. The H. W. Wilson Co., New York, N. Y.

Free medical care has been a highly controversial subject ever since the idea was first introduced. In November of last year, President Truman sent Congress a request for legislation leading toward a national health program. This paved the way for the well-known Wagner-Murray-Dingell Bill which possessed such far-reaching social significance. It was first instrumental in making the public conscious of the facts concerning national health.

It is the purpose of this volume to present the most effective viewpoints of the authorities writing on both sides of the problem. There are many who are either for or against the subject but there are an equal number who present opinions in varying degrees which reflect the knowledge of modern needs, expanding institutions and a new concept of public service.

This volume is a condensation and compilation of the many excellent articles which have appeared in the scientific, medical and lay publications in the past few years. The first section presents those articles which discussed the problem from a general viewpoint,

whereas the second and third sections present those discussing the affirmative and negative stands, respectively.

Since this subject is one of frequent debate, this volume should prove a valuable reference work. For those who wish to pursue the subject more deeply an extensive bibliography, divided into the same classifications as the text, is presented.

This book is recommended to anyone interested in learning the pros and cons of the subject of socialized medicine without the effort of attempting to assemble all of the printed literature on the subject.

M. O. H.

What Industry Owes to Chemical Science. Based on a scheme by Richard B. Pilcher and Frank Butler with fifty contributors. Issued by the Authority of the Council of the Royal Institute of Chemistry. 372 pages incl. index. American ed. Chemical Publishing Co., Brooklyn, N. Y. Price: $5.00.

The first edition of "What Industry Owes to Chemical Science" consisted of twenty articles contributed to *The Engineer* in 1916-17. The purpose was to supply an answer to the question—"What is the place of the chemist in practical life and what part has he taken in industrial and social development?"

The majority of people do not realize that chemistry plays such an important part in the national life. Its place in the future will be one of even greater importance. Hardly any important industrial concern can be successful without a staff of chemists. Even the smallest concerns find it necessary to retain the services of a full-time chemist or a part-time consultant.

The list of subjects treated in this volume include a great variety which are classified under the general headings: agriculture, food, water supplies and sanitation, pharmaceutical products, soaps, waxes and glycerin, disinfectants, antiseptics and preservatives and many other topics.

Fifty-three well-known English authors contributed their best dissertation to this book which in each chapter presents a fascinating story of the contributions of chemical discoveries to the development of a most important industry serving the public comfort and raising the standard of living.

M. O. H.

Actions and Uses of Drugs. By Windsor C. Cutting, M. D. 326 pages incl. index plus 10 pages for notes. Stanford University Press, Stanford University, Calif. Price: $3.00.

This is a textbook designed primarily for nurses who in their training course must of necessity study pharmacology and therapeutics simultaneously. Medical students because of their more extensive period of training usually study each subject separately and in sequence. The limited scope of training and shorter period of time involved in the nursing course forces the subjects to be more condensed. Nurses consequently are learning the action of the drug on the body at the same time that they learn its therapeutic uses.

The author, in this book, has attempted to coordinate the two aspects by discussing the drugs individually with emphasis on the therapeutic applications. Wherever possible, the individual drugs have been grouped together according to the disease or region of the body upon which they are effective. In those cases where it is necessary to better understand the use of the drug, the abnormal physiology of the disease is briefly considered.

In separate chapters are discussed allergy and hypersensitivity, immunity and toxicology. An extensive appendix presents the calculation of solutions and measurements of doses, metric and English equivalents, abbreviations, dosages and a brief list of reference works.

The pharmacist as well as the nurse and students in particular will find this book of value either for study or reference.

M. O. H.

Penicillin—Its Properties, Uses, and Preparations. Published by direction of the Council of the Pharmaceutical Society of Great Britain. vii + 199 p. incl. index. Price 10s. 6d. Postage 6d. The Pharmaceutical Press, 17 Bloomsbury Square, W. C. 1 London.

This book was prepared due to the very numerous requests for information on penicillin received by the editor of the *Pharmaceutical Journal*. No authorship of the book is stated but one suspects that a number of very well-informed workers contributed in the preparation.

Possibly no drug in history has received the attention given penicillin and the amount of material published about it in the last five years would almost fill a library. Unfortunately, much that has been published is now obsolete or even erroneous and, consequently, there is great need for just this sort of book giving the latest authentic information on a drug which must be thoroughly understood if it is to be used or dispensed with full benefit to the patient.

This book in its one hundred ninety-nine pages does an admirable job of presenting what is now known about penicillin.

The subject matter is divided as follows:

Historical Summary
Commercial Manufacture
Chemistry and Chemical Properties
Stability
Standard, Unit and Methods of Assay
Pharmacology
Clinical Use
Pharmacy and Pharmaceutical Preparations
Legal Considerations.

The relationship of United States and British units and standards is clearly defined, which is very helpful. Dosage schedules which are given are a little on the conservative side, according to our practice, but this is the result of our ample supply situation together with the almost total lack of toxicity shown by penicillin.

The book is highly endorsed to American pharmacists and others who wish to find some pertinent data about penicillin without resorting to the plethora and confusion found in the voluminous literature on the subject.

L. F. T.

The National Formulary, Eighth Edition, 1946 (N. F. VIII). Prepared by the Committee on National Formulary under the supervision of the Council by authority of the American Pharmaceutical Association. xxxviii + 850 p. incl. index. Mack Printing Co. $7.50.

The new National Formulary together with the U. S. P. XIII become official on April 1, 1947. By close cooperation those respon-

sible for each official compendium arrange the text and style of each book in an almost identical pattern. This is a very great advantage to the worker who uses both books and one can remember the confusion sometimes resulting when the two books were patterned differently.

The arrangement of text in the new National Formulary is praiseworthy since English titles are now given precedence over the Latin and preparations will be found immediately following their chief constituent. From both the teaching standpoint and the use of the book by physician and pharmacist this is a decided advantage, in spite of a few die-hard critics.

The scope of the National Formulary is based on a different premise than that used by the Pharmacopoeia. The National Formulary Committee considers for adoption drugs not in the Pharmacopoeia but which are either extensively used or which show therapeutic promise. It has long been a proving ground for drugs later recognized in the Pharmacopoeia. In that it establishes formulas and standards for many useful drugs, the National Formulary is a valuable contribution to both pharmacy and public health and therefore our dual system of official books is fully justified.

Chairman Powers and his Committee deserve praise for the fine character of the eighth edition and for their courage in deleting dozens of archaic drugs and preparations. This was done in the face of strong opposition largely from proprietary manufacturers. A few other drugs might well have been added to the list of deletions, e. g. ovary and anterior pituitary. By all known physiological tests these drugs are as inactive orally in their endocrine effect as powdered meat.

Some very useful new drugs and preparations have been added. The pharmacist will find oleyl alcohol, dioctyl sodium sulfosuccinate, glyceryl monostearate, propylene glycol, sodium alginate, etc., very useful in formulations, and the physician will find an abundance of very useful drugs with well established pharmacology.

The eighth edition sets a new standard of achievement for which the American Pharmaceutical Association can justly be proud.

L. F. T.

A Note on Rutin

I am very interested in the article entitled "Rutin and Capillary Fragility" by Elof F. Johnson, M. Sc., published in the *American Journal of Pharmacy* for May, 1946, pages 164-175.

In view of the importance which Rutin has just attained in your country and the large estimated quantities required annually for possible nutrition requirements, I have deemed it advisable to draw your attention to the sources of Rutin in Australia.

One of my predecessors, the late H. G. Smith, directed attention to the large amount of yellow dye material obtained from the leaves of *Eucalyptus macrorhyncha.* He named it Myrticolorin (see *Journal Chemical Society,* 1898, page 697). Smith did not recognize the material as identical with Rutin.

It was subsequently shown that Myrticolorin was identical with Rutin. A further note on the occurrence of Rutin in the leaves of Australian plants was published by F. R. Morrison in the *Journal and Proceedings of the Royal Society of New South Wales,* Vol. LV (1921), pages 210-214. The paper is entitled "The Occurrence of Rutin in the Leaves of the *Boronia* (N. O. *Rutaceæ*).

Summarizing the results obtained to date, the following yields should be noted, viz.:

Eucalyptus macrorhyncha, 7 to 8½ per cent on dried leaves.
Boronia serrulata, dried leaves 6.6 per cent.
Boronia thujona, dried leaves 5 per cent.

The occurrence of Rutin has been noted in the leaves of many other Australian plants belonging to the N. O. Rutaceæ and Myrtaceæ.

Yours sincerely,

A. R. PENFOLD, Director,
The Museum of Technology and Applied Science, Sydney, Australia.